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Synthesis and Biological Evaluation of Some Heterocyclic Derivatives of N-Aryl-3-Cyclopropyl-3-Oxo-Propanamide Analogue

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Abstract: ***The synthesis and pharmacological evaluation of dihydropyridines are described, these compounds have been found to possess very promising αa1-adrenergic and calcium channel blocking activities which are clinically used in the treatment of hypertension and some other cardiac disorders, calcium channel blocker are increasingly becoming the drug of primary treatment supported by β-blockers. It is fore there worth while to synthesize and evaluate compounds having pharmacophores of both the types of drugs. Dihydropyridine derivatives like some new Methyl-5-arylamido-4-(o-chlorophenyl)-6-cyclopropyl-2-methyl-1,4-dihydropyridine-3-carboxylate derivatives of type (2a-l) have been synthesized by the condensation of N-Aryl-3-cyclopropyl-3-oxo-propanamide of type (1a-l) and methyl-3-amino crotonate with o-chlorobenzaldehyde. All the prepared compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.***

Keywords : N-Aryl-3-cyclopropyl-3-oxo-propanamide, 1,4-Dihydropyridine , Antimicrobial activities.

I. INTRODUCTION

1,4-Dihydropyridine is the significant subclass of pyridines, the best known heterocyclic compounds which are associated with number of pharmacological activities. 1,4-Dihydropyridines, whether symmetrical or unsymmetrical are expected for their cardiovascular and other pharmacological properties. Sufficient literature is available regarding structure activity studies[1-5]. The DHP nucleus is common to numerous bioactive compounds which include various vasodilator, antihypertensive, bronchodilator, ant atherosclerotic, hepatoprotective, antitumor, ant mutagenic, geroprotective and antidiabetic agents[6-11]. 1,4-Dihydropyridines are not only intermediates for the synthesis of pyridines, but are also an important class of N-heterocycles[12-13] an example is the coenzyme NADH. Some derivatives have found application in the therapy of high blood pressure and angina pectoris[14]. For that reason different synthetic methods[15-16] for the synthesis of 1,4-dihydropyridines has been the subject of intensive research and industrial use.

The structure of synthesized compounds were assigned based on Elemental analysis , I.R. ^{1}H-NMR and Mass spectral data. The antimicrobial[17] activity was assayed by using the cup-plate agar diffusion method [18] by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities against varieties of bacterial strains such Staphylococcus aureus, Bacillus subtilis, Aero genes, P. aeruginosa and fungi Aspergillus niger at 40 µg concentration. Standard drugs like Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and Griseofulvin were used for comparison purpose (Table-1).

II. EXPERIMENTAL SECTION

Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm^{-1}) were recorded on SHIMADZU FTIR 8400 Spectrophotometer ; Frequency range : 4000-400 cm-1 (KBr disc) and , ^{1}H-NMR spectra on Bruker spectrometer (200MHz) using TMS as an internal standard, chemical shift in δ ppm.

A. General procedure for the Preparation of Methyl-5-arylamido-4-(o-chlorophenyl)-6-cyclopropyl-2-methyl-1,4 dihydropyridine-3-carboxylate (2a-l) :

A mixture of 3-Cyclopropyl-*N*-(*p*-nitrophenyl)-3-oxopropanamide (3.70gm 0.01mol) and methyl-3-amino crotonate (1.15gm, 0.01mol) in methanol was refluxed in water bath for 18hrs. Cooled down reaction mixture at room temperature and stand by 24 hrs. The resulting solid mass was filtered and washed with methanol. Recrystallized the product in methanol. Yield 45 %, m.p. 200°C. Anal. Calcd. for $C_{24}H_{22}N_3O_5Cl$ Calcd: C,61.61; H, 4.74; N,8.98 %, Found: C,61.78; H,4.88; N, 9.13 %. Similarly, other Methyl-5-arylamido-4-(*o*-chlorophenyl)-6-cyclopropyl-2-methyl-1,4-dihydropyridine-3-carboxylates were prepared. The physical data are recorded in Table No. 1

B. Methyl-5-arylamido-4-(o-chlorophenyl)-6-cyclopropyl-2-methyl-1,4-dihydropyridine-3-carboxylate (2a-l) :

Yield 45 %, m.p. 200 ^{0}C; IR(KBr) : Alkane C-H str. (asym.) 2965, -CH_3 C-H str. (sym.) 2847, C-H def.(asym.) 1422 , C-H def. (sym.) 1367, Aromatic C-H str. 3022, C=C str. 1596, C-N 1300, N-H str. 3379, Carboxamide C=O str. 1653, N-H str. 3296, Ether Ar-O-C str. 1237, Ester C=O str. 1711 , Nitro N=O str. 1515 , NO_2 str. 1367, Halide C-Cl str. 734. cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 0.65-0.79 (m,4H, HC-($\underline{CH_2}$)$_2$, 2.06-2.08 (m, 1H, $\underline{HC}$-(CH_2)$_2$), 2.38 (s, 3H, Ar-CH_3), 3.05 (s, 3H, CO-O$\underline{CH_3}$), 5.39 (s, 1H, pyr-C-H), 7.05-8.11 (m, 8H, Ar-H), (overlapped) (1H, N-H), 9.67 (s, 1H, N-H). Mass m/z 467 . M.F.: $C_{24}H_{22}N_3O_5Cl$.

Scheme-1

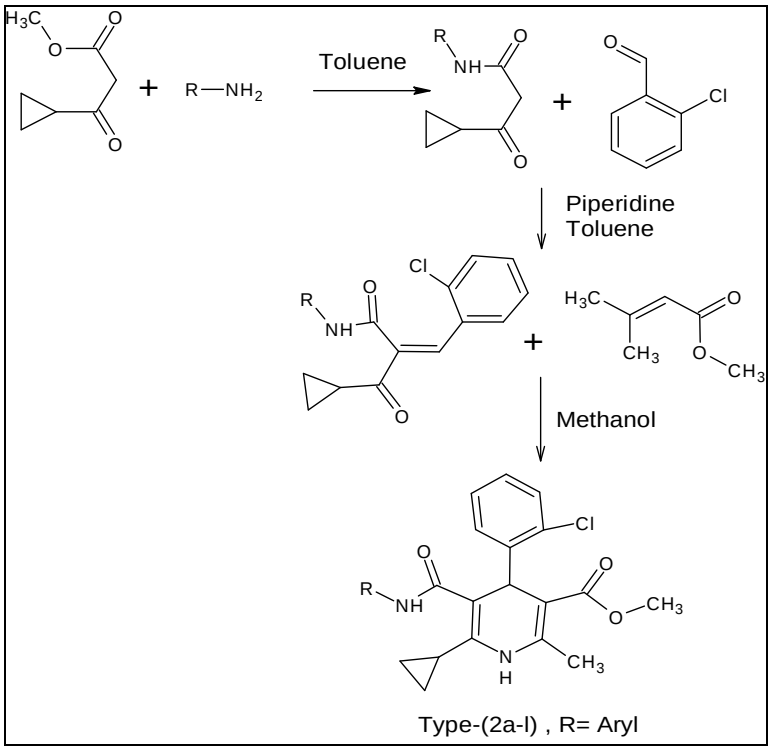


Table-1

Characterization data of the compounds (2a-l):						
compd no.	R	Molecular Formula	Mole.Wt.	M.P. (^{0}C)	Nitrogen %	
					Calcd	Found
2a	C_6H_5-	$C_{24}H_{23}N_2O_3Cl$	422.5	108	6.62	6.80
2b	3-Cl-C_6H_4-	$C_{24}H_{22}N_2O_3Cl_2$	457.5	70	6.13	6.31
2c	4-Cl-C_6H_4-	$C_{24}H_{22}N_2O_3Cl_2$	457.5	50	6.13	6.31
2d	3,4-(C l)$_2$-C_6H_3-	$C_{24}H_{21}N_2O_3Cl_3$	491	95	5.70	5.96
2e	2,6-(Br)$_2$-4-NO_2-C_6H_2-	$C_{24}H_{20}N_3O_5Br_2Cl$	625.5	120	6.72	6.89
2f	4-F-C_6H_4-	$C_{24}H_{22}N_2O_3FCl$	440.5	90	6.35	6.52
2g	3-CH_3-C_6H_4-	$C_{25}H_{25}N_2O_3Cl$	436.5	53	6.41	6.60
2h	4-CH_3-C_6H_4-	$C_{25}H_{25}N_2O_3Cl$	436.5	115	6.41	6.60
2i	4-OCH_3-C_6H_4-	$C_{25}H_{25}N_2O_4Cl$	452.5	110	6.18	6.60
2j	2-NO_2-C_6H_4-	$C_{24}H_{22}N_3O_5Cl$	467.5	65	8.98	9.13
2k	3-NO_2-C_6H_4-	$C_{24}H_{22}N_3O_5Cl$	467.5	163	8.98	9.13
2l	4-NO_2-C_6H_4-	$C_{24}H_{22}N_3O_5Cl$	467.5	200	8.98	9.13

C. Antibacterial Activity

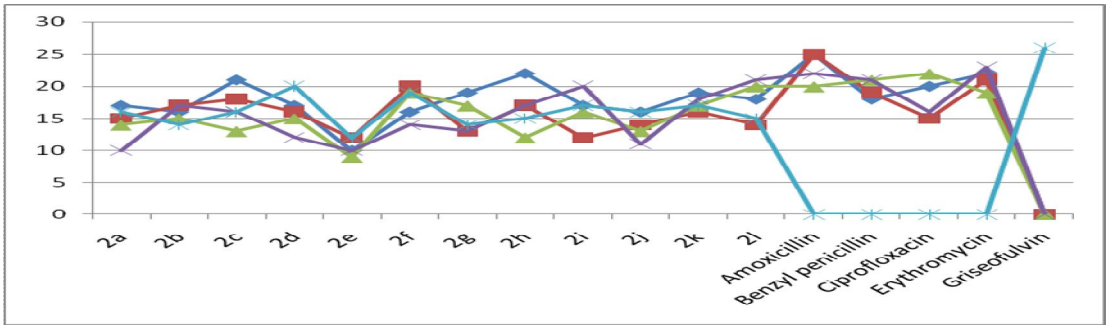
It has been observed from the microbiological data that all compounds **(**2a-l) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains. How ever the maximum activity was observed in compounds (2c), (2f) against S.aureus. The significant activity was observed in compounds (2c), (2h) against B. subtilis. The maximum activity was displayed by the compounds (2f), (2l), against Aero genes. The compounds (2i), and (2l) were comparatively more effective against P. aeruginosa.

D. Antifungal Activity

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds (2d), (2f) against *A.niger*.

The antibacterial activity was compared with standard drug viz. Ampicillin, Benzyl penicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Griseofulvin.

Table-1 Antimicrobial activity : (zone of inhibition in mm)



III. RESULTS AND DISCUSSION

Dihydropyridine derivatives like some new Methyl-5-arylamido-4-(*o*-chlorophenyl)-6-cyclopropyl-2-methyl-1,4-dihydropyridine-3-carboxylate derivatives of type (2a-l) have been synthesized by the condensation of N-Aryl-3-cyclopropyl-3-oxo-propanamide of type (1a-l) and methyl-3-amino crotonate with o-chlorobenzaldehyde. The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR ,[1] H-NMR , and mass spectral data.

IV. CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds. Which show significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

V. ACKNOWLEDGMENT

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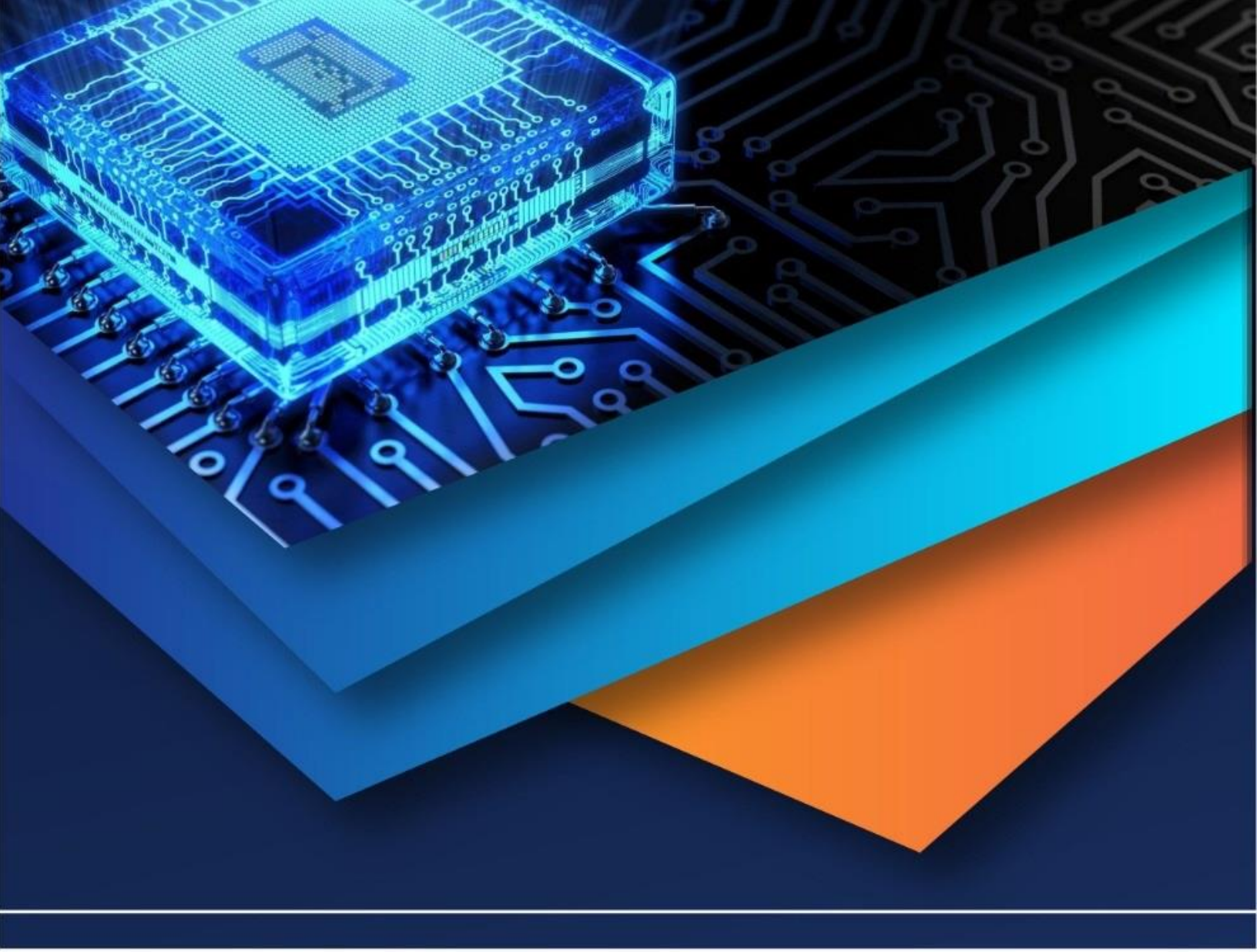

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